Japan Kokai Patent (A)

Kokai Patent Number: Sho- 57 – 114512
(*Note by translator: Sho means Showa era, Sho 57 corresponds to 1982*)
Date of Kokai (*Note by translator: Date of Open to public*): July 16, 1982

(*Note by translator: There are two stages in the Japanese patent system. The first stage is so-called Kokai Patent which means the patent applied by a applicant(s) is published to open without any examination, but it is not an actual patent. After the Kokai Patent is examined by the Patent Office in Japan, the actual Patent is notified as the Kokoku Patent which is the second stage.*)

Anti-diabetic agents containing (3-dimethyl carbamoxyphenyl) trimethyl ammonium derivatives

Appl. No: Sho-56-184012
Date of File: Feb. 20, 1980
Appl. No: Divided patent application of Sho-55-19893

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DETAILS

1. Title of the Invention:

Anti-diabetic agents containing (3-dimethyl carbamoxyphenyl) trimethyl ammonium derivatives

2. Claims:

(1) Anti-diabetic agents containing (3-dimethyl carbamoxyphenyl) trimethyl ammonium

derivatives as active components described in Fig. 1 as a general formula in which R represents either methylsulfate ($CH_3SO_4^-$) radical or bromine atom.

(*Note by translator: Sorry I don't draw the chemical structure in this paper, but I will send it by FAX if it's necessary. Please let me know.*)

3. Details of this Invention

This invention relates to anti-diabetic agents containing (3-dimethyl carbamoxyphenyl) trimethyl ammonium derivatives as active components described as a general formula.

In this formula, R represents either methylsulfate ($CH_3SO_4^-$) radical or bromine atom.

Compounds (Note: *will be described as "this compound" in this translated patent*) shown in the general formula described above are known compounds, and have been known as an effective component of an excitant of parasympathetic nerve system.

The inventor discovered that this compound had a reducing activity of sugar levels in blood and that its side effects were low even by a long-term administration.

The invention is explained in detail as follows;

Its toxicological and pharmacological characteristics will be explained later.

(1) Acute toxicity

Acute toxicity of this compound has been reported as shown in Table 1.

Table 1 Acute Toxicity of this Compound

Compound tested	Animals used	Method of Administration	LD_{50} (mg/kg)
This Compound (R in formula I is Br.)	mouse	p.o.	7.5
		i.v.	0.165
	cat	p.o.	7.449
		i.v.	0.171
This compound (R in formula I is methylsufate radical)	mouse	p.o.	12-16
		s.c.	1
		i.v.	0.3-0.4
	rabbit	s.c.	0.5-0.75
		i.v.	0.25

(2) Reducing Activity of Blood-Sugar Levels

The rats tested as animal models were obtained by the following procedure. Eighty mg/kg of Streptozotocin was injected into abdominal cavity of Wistar rats and a week after the injection, positive results on their sugar levels in urine and in blood were recognized. Then insulin was administered to these rats above described and after that, reduction of sugar levels in urine and blood were found in these rats. Several days after the treatment, high levels of sugar in urine and blood were confirmed. The following experiments were carried out using these animal models.

This compound was dissolved in distilled water and 0.5 mg/kg (of rat's weight) of this compound in solution was administered orally.

Each blood sample was collected from vein in their tails and the level of glucose in the sample was determined enzymatically using RaBA kits. The results are shown in Table 2.

Table 2 Blood-Sugar Reducing activity of the Compound

Compound tested	Reduction of Blood-Sugar Level(mg/dl)	
	3 hr	6 hr
This compound (R in formula I is Br)	-75	-42
This compound (R in formula I is methylsulfate radical)	-6	-11

Dosage: 0.5 mg/kg by p.o.

Formulation of this compound will be described as follows.

When this compound is used as an anti-diabetic agent, it can be used as the most effective form, depending upon symptoms of the disease, and also it can be used as a single form or as a mixture with diluents and/or with other agents which have been allowed to use.

It can be administered orally or non-orally. Therefore, any formulation for oral or non-oral administration can be applied.

This compound can be supplied based on its administration unit. The medication contains effective amounts of this compound and its formulation can be employed as various forms, such as powder, granule, tablet, sugar-coated tablet, capsule、suppository, suspension, emulsion, ampoule and injection. Solid, liquid or semi-solid type of diluents are used. For example, the following diluents can be applied; excipients, fillers, bounding agents, moisturizers, surface active agents, emulsifiers, flavors, preservatives, liquefiers and solvents. Furthermore, either one of them or more than one of them can be used.

The anti-diabetic agents in this invention can be manufactured by any known processes. The active component (this compound) in the compositions employed in this invention can be used in the range of 0.001 – 50 wt% in general, more preferably in the range of 0.01-5 wt%.

The anti-diabetic agents in this invention can be administered to human beings and animals either orally or non-orally, more preferably orally. Its oral administration includes

sublingual administration. Its non-oral administration includes injection, for example hypodermic (subcutaneous), intramuscular, intravenous and dropping injections.

Dosage of the anti-diabetic agent in this invention depends on either for animals or for human beings, and also depend on age, individual variation and/or condition of patients, and therefore there are some cases which the dosage is more or less than the range described below. But in general, its dosage for human by oral administration is 0.01-500 mg per 1 kg of weight in a day, preferably 0.1-50 mg and that by non-oral administration is 0.0001-1 mg per 1 kg of weight in a day, preferably 0.001-0.1 mg through 1 to 4 times fractional administration.

Examples are shown below. "Part" described in these examples means weight.

Example 1:

This compound (R in formula I is Br)	1 part
Precipitated calcium carbonate	25 parts
Magnesia alumina hydrate	45 parts
Starch	30 parts

These materials are mixed uniformity and kneaded, crushed and tableted. After drying and sieving, the granule agent is prepared.

Example 2:

This compound (R in formula I is methylsulfate radical)	0.5 part
Starch	20 parts
Lactose	35 parts
Crystalline cellulose	40 parts
Polyvinyl alcohol	3.5 parts
Water	30 parts

These materials are mixed uniformity and kneaded, crushed and tableted. After drying and sieving, granules are prepared. Four parts of Calcium stearate is added to 96 parts of the dried granules and the mixture is tableted by compressing.

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